UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,738	02/18/2004	Andreas H. Sarris	480208.401C3	1671

500 7590 07/20/2006

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,738	SARRIS ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 5-23-06 is acknowledged.

Claims included in the prosecution are 71-86.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 71-79 and 81-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb (5,741,516) of record by itself or in combination with Mehlhorn (5,762,957) or vice versa (Mehlhorn in view of Webb).

Webb discloses a method of preparation of liposomes containing vinca alkaloids such as vinblastine and vincristine (sulfate). The method involves, a) preparing vinca alkaloid solution b) preparing liposomes containing sphingomyelin and cholesterol with an acidic interior (citrate buffer); 2) adding vincristin sulfate to the external medium; 3) adding disodium hydrogen phosphate to the external medium to create a pH gradient with an external pH of 7.2 to 7.6. The transmembrane gradient created loads vincristine sulfate into the liposomes (abstract, col. 6, line 8 through col. 7, line 12, Examples, Examples 1-2 in particular and claims). What is lacking in Webb is the teaching of the supply of the vinca alkaloid solution (step a in the method), liposomes (step b) and disodium phosphate solution in the form of a kit. However, supply of the reagents to prepare vincristine sulfate loaded liposomes just before use by the method taught by

Webb would have been obvious to one of ordinary skill in the art with a reasonable expectation of success,

Mehlhorn teaches a method of loading liposomes with drugs and a kit for such a method. The method involves preparing the liposomes with acidic interior (citrate buffer), adding a solution to make the exterior of the liposomes basic to create a transmembrane gradient and loading the chemical species (drug). According to Mehlhorn, the reagents, chemical species solution, liposomes and the basic solution are to be supplied in the form of a kit. By such a method according to Mehlhorn, the encapsulation can be done quickly and easily. The fear of degradation of the vesicles and leakage of the chemicals prior to administration need not be a concern, since the chemicals are easily encapsulated in the vesicles usually just before use, and the vesicles containing the chemical can be immediately delivered without further purification or other treatment (abstract, col. 2, line 9 through col. 4, line 61, col. 6, line 12 through col. 10 line 6, Examples and claims). What is lacking in Mehlhorn is the teaching of vinca alkaloids as the chemical species.

It would have been obvious to one of ordinary skill in the art to supply the reagents of Webb in the form of a kit since Mehlhorn teaches that kits can be used for the loading of liposomes with the chemicals by the same method just before use and advantages of such kits. Alternately, the use of vinca alkaloids as the chemical species in the kit of Mehlhorn would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success since Webb teaches the loading method, which is the same as Mehlhorn.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Webb does not teach or suggest a kit comprising three separate vials containing components for use in preparing a liposomal vinca alkaloid formulation, as presently claimed and that instead Webb teaches a liposomal vinca alkaloid formulations having increased drug retention and enhanced stability. According to applicant, Webb is silent regarding kits per se, but teaches that the drug-loaded liposomes may be prepared as pharmaceutical compositions and then packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. Further according to applicant that these packaged pharmaceutical compositions comprise liposomes already loaded with drug, e.g., vinca alkaloid. These arguments are not persuasive. The components in Webb in the method of preparation of liposomes containing vinca alkaloids are the same as in instant invention. That is, liposomes comprising sphingomyelin and cholesterol, vinca alkaloid solution and disodium hydrogen phosphate solution with a higher pH. Although Webb suggests the sterilized aqueous compositions or lyophilized compositions for convenience, there is nothing in Webb to suggest that the solutions themselves should not be supplied in a kit form. Supply of the components in a kit form in a highly developed field of liposomes is within the skill of the art, especially when Webb teaches on col. 5, lines 30-35 that sphingosomes containing sphingomyelin and cholesterol are stable to acid hydrolysis. The skill of supplying empty acidic liposomes and the drug containing solution in a kit form is clearly evident from the reference of Mehlhorn. If empty acidic liposomes are

stable as evident from Mehlhorn one of ordinary skill in the art would expect much more stability of empty sphingosomes when supplied in kit form from the teachings of Webb who describes these liposomes as more stable to acid hydrolysis.

Applicant argues that with respect to vincristine, it was known prior to the filing of instant application that vincristine is a relatively labile molecule with an optimal pH for stability of 3.5 to 5.5 and therefore, the liposomal vincristine formulations described by Webb, which have an acidic intraliposomal pH, would have been expected to provide a stable environment for vincristine. According to applicant, this is yet another reason why the skilled artisan would lack motivation based upon Webb to modify its teachings of pre-loaded liposomal formulations to remove the drug from the liposome and provide it in a separate container. These arguments are not persuasive since once loaded, the vincristine amounts within the liposomes is a constant factor whereas, if the liposomes are empty and the compound is loaded just before use, one could vary the amounts of encapsulated vincristine. Therefore, one of ordinary skill in the art would be motivated to supply empty liposomes and vincristine separately.

Applicant argues that Mehlhorn describes two kits and the two-component embodiment in Mehlhorn is the most relevant to the instant claims. According to applicant, this two component kit includes 1) a solution comprising empty liposomes in an acidic buffer, and 2) a solution comprising a basic buffer, wherein the drug is present in the solution that affords it the greatest chemical stability and therefore, in the context of vincristine, which was known to be more stable in an acidic environment, the drug would be present in the solution containing the liposomes. These arguments are not

persuasive. First of all, Mehlhorn is combined to show the knowledge in the art to supply material in the kit form where the drug is loaded using a gradient. Secondly, it is within the basic skill of the art to supply the active agent separately from the disodium hydrogen phosphate solution taught by Webb if the active agent is labile in this alkaline medium. It should be noted that Webb adds an acidic solution of vincristine first to the empty liposomes and then adjusts and creates the pH gradient by adding the alkaline solution of disodium hydrogen phosphate. Therefore, one of ordinary skill in the art would supply the active agent such as vincristine in the acidic solution and not in the basic solution if the initial experiments determine the lability of the compound in alkaline pH.

Applicant's arguments that the loading method described by Mehlhorn is distinct from the loading method performed using the claimed kits. According to applicant, the method of Mehlhorn involves preparing liposomes having a pH gradient across their membranes, wherein the pH of the solution exterior of the liposomes is not a physiologically benign pH and that only upon addition of a further solution that the pH is adjusted to a physiologically benign pH and in contrast, the method of present invention involves preparing liposomes having a pH gradient across their membranes, wherein the pH of the solution exterior of the liposomes is physiologically benign pH. These arguments are not persuasive since adding enough basic solution to bring the external medium to neutral or adjusting the external medium later to bring it to neutral are obvious manipulations practiced by an artisan in the highly developed field of chemistry or biological sciences.

3. Claims 80 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb (5,741,516) by itself or in combination with Mehlhorn (5,762,957) or vice versa (Mehlhorn in view of Webb), further in view of Lenk (5,262,168).

The teachings of Webb, and Mehlhorn have been discussed above. What is lacking in these references is the teaching of the use of a cryoprotectant such as mannitol.

Lenk while disclosing prostaglandin liposomal compositions teaches that the liposomes can be loaded using a pH gradient and that the liposomes can be lyophilized using cryoprotectant such as mannitol. An aqueous solution containing the drying protectant is added to encapsulate the drying protectant (abstract, col. 4, lines 15-20, col. 9, line 53 through col. 10, line 6).

To include a drying protectant such as mannitol in the aqueous solution of the kit taught by Mehlhorn, if the goal is to lyophilize the liposomes, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Lenk teaches such a use in liposome formulations.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding Webb and Mehlhorn. Applicant argues that Lenk fails to remedy the deficiencies of Webb and Mehlhorn. These arguments are not persuasive since Lenk is combined for its teachings of the inclusion of cryoprotectants during lyophilization process.

The declaration submitted by Dr. Madden has been fully and carefully evaluated, but are not found to be persuasive. Dr. Madden states that the studies indicate that the

shelf life of the liposomal vincristine described in Webb is considered less than desirable for certain commercial applications. These arguments are not persuasive since instant claims are drawn to kits containing the empty liposomes and the active agent separately and not drawn to liposomes containing vincristine. The issue here is the components in the form of a kit and not whether the liposomes of Webb or desirable or not.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK